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Appendix E1

The Inclusion, Exclusion Criteria, and Details of Patient Clinical Information

Our inclusion criteria included 1. Drug-resistant epilepsy for more than 2 years with age from 16 years to 60 years. 2. Seizure semiologies, scalp video-EEG findings and memory deficit pattern that are consistent with the characteristics of amygdalo-hippocampal seizure proposed by the International League of Anti-Epilepsy (ILAE). 3. Unilateral or bilateral hippocampal sclerosis (HS) reported by neuroradiologists from the First Affiliated hospital of Zhejiang University based on a visual inspection approach. Patients were considered to be MR imaging-negative HS when the MR imaging was reported MR imaging-negative, brain positron emission tomography (PET) showed hypometabolism in one temporal lobe, or symmetric bilateral temporal lobe hypometabolism, or asymmetric bilateral temporal lobe hypometabolism more severe on one side. 4. No other structural lesions were found on brain MR imaging.

Our exclusion criteria included 1. Patients are < 16 years or > 60 years; 2. Non-drug-resistant epilepsy. 3. Seizure semiologies, scalp EEG findings and clinical-electroencephalographic correlations suggest neo-cortical epilepsy and generalized epilepsy. 4. Patients reported MR imaging negative, if brain PET shows normal metabolism or hypometabolism extending beyond temporal lobes. 5. Structural lesions other than HS found on brain MR imaging. 6. Patients with claustrophobia.

Nine of these patients were diagnosed with structural lesions other than HS and excluded. Further presurgical evaluations were implemented for the remaining 36 patients. Two of these were diagnosed as frontal lobe epilepsy and one was diagnosed as focal epilepsy. In total, we excluded 12 patients. We included thirty-three patients (23 females and 10 males, 16–60 [mean 32.6] years old) with drug-resistant TLE-HS. All patients had been pharmaco-resistant for more than 2 years and were admitted for presurgical evaluation. Prior to the recruitment, the diagnosis of MTLE and the lateralization of seizure onset were hypothesized on the basis of the results of extensive presurgical workup including scalp video-EEG monitoring (seizure semiology, interictal epileptic discharges and ictal EEG patterns), MR imaging with T_1 weighted magnetization-prepared rapid gradient echo (MPRAGE), T_2 weighed turbo spin-echo and FLAIR sequence, and cranial PET scan. The origin of seizure onset was defined at the seizure conference based on concordance of semiological, radiologic and electrophysiological findings. After reviewing the relevant clinical data, two epileptologists (WK and WDC, with 15 and 7 years of experience in epileptology, respectively) made the diagnosis of unilateral TLE-HS on the basis of typical ictal semiologies (episodic unresponsiveness with auras of abdominal discomfort, déjà vu or fear), interictal spikes with maximal negativity predominantly over left or right temporal region on scalp video-EEG as well as unilateral hippocampal volume loss and T_2 hyperintensity on MR imaging. Similarly, bilateral TLE-HS was diagnosed on the basis of the recorded seizures originated from bilateral temporal lobe independently on semiology and ictal EEG pattern and bilateral temporal lobe spikes interictally.

Data Acquisition and Image Reconstruction

All MR measurements were performed on a 3T Siemens Prisma scanner (MAGNETOM Prisma, Siemens Healthineers, Erlangen, Germany) with a 20-channel head coil, and the total image acquisition time for each subject was about 18 minutes.

The conventional MR imaging protocol included T_1-and T_2-weighted and FLAIR-sequences. D magnetization-prepared rapid gradient echo (MPRAGE) with an isotropic resolution of 0.93 mm was acquired for T_1 weighted imaging, and two planes (transverse and coronal views) of 2D turbo spin-echo (TSE) with an in-plane resolution of 0.43 mm and a slice thickness of 4 mm were acquired for T_2 weighted imaging. Coronal FLAIR was acquired with an in-plane resolution of 0.90 mm.

Subsequently, 2D MRF was acquired with whole temporal lobe coverage in about 2.5 minutes in each orientation (transverse and coronal views). The MRF sequence was based on an inversion-recovery fast imaging with steady-state precession sequence (FISP-MRF). Twenty slices with a slice thickness of 3 mm that covered the temporal lobe of subjects were acquired in both transverse and coronal orientations. Coronal slices were angulated perpendicular to the hippocampal long axis, and a paramedian slice displaying the hippocampal long axis was used for planning. Scanning covered the region from the temporal pole to the hippocampal tail. Axial slices were angulated along the AC-PC line, covering the area from the fourth ventricle to thalamus. The TRs varied from 10 to 12 msec using a Perlin noise pattern, and the flip angles (FAs) of sinusoidal shape ranged from 5 to 80 degrees to drive the magnetization into a persistent transient state for each slice of MRF acquisition with TE fixed to 2.5 msec for all frames. Variable density spiral (VDS) k-space sampling trajectory which consisted of 30 interleaves, 1200 points per interleaf with zero-moment nulling was utilized for acquisition. Each interleaf was rotated by 12 degrees in each TR. Six hundred frames were acquired per slice with the total acquisition time about 2.5 minutes for 20 slices in each orientation. An in-plane spatial resolution of 1.2×1.2 mm^2 was achieved for the reconstructed images in a FOV of 240×240 mm^2.

The corresponding dictionary was generated using extended phase graph (EPG) algorithm. T_1 and T_2 values in the dictionary ranged from 20 to 5000 msec and 20 to 2000 msec were sampled using 160 points, with values finely sampled at 20 msec intervals of T_1 and 2 msec intervals of T_2 around the expected T_1 and T_2 values of white matter and gray matter (T_1=[20:20:3000, 3200:200:5000] ms and T_2=[20:2:140,145:5:300,310:15:1000,1050:50:2000] ms). Bloch-simulation based slice profile correction was applied for dictionary generation to obtain accurate template matching and parameter estimation. The final T_1, T_2 and PD maps were recognized simultaneously after reconstructing the time-series images using a sliding-window algorithm. All reconstruction and pattern recognition algorithms of MRF were implemented in the same computer environment (Red Hat Enterprise, Linux server with 17 Intel Xeon 2.8 GHz CPUs) using MATLAB R2014a (The MathWorks, Inc., Natick, MA) toolbox.

Detailed steps for detection of HS lesions based on MRF-defined suspicious components

HS lesions were detected using the following steps: (i) voxel by voxel segmentation was applied using rTF-MRF method. Each voxel was segmented into four components including gray matter (T_1/T_2=1250/105 ms), white matter (T_1/T_2=820/50 ms), cerebrospinal fluid (CSF)

(T_1/T_2=3500/2000 ms) and a suspicious component (T_1/T_2 selected from MRF results). The T_1 and T_2 values of white matter, gray matter and CSF components were calculated and averaged from typical regions of 30 healthy volunteers, while the T_1/T_2 values of the suspicious component were selected by observing abnormal T_1 and T_2 values from MRF results and ranged between CSF and gray matter component, which were regarded as the prior information for HS patients. All of these components were substituted into equation (1). (ii) Since HS is known to have prolonged T_1 and T_2 values, abnormal regions would appear as suspicious compartments. For detecting bilateral HS lesions, the histograms of T_1 and T_2 values in the hippocampus were plotted to identify the suspicious component. If prolonged T_1 and T_2 values in hippocampus were found, the corresponding regions were marked as suspicious components. (iii) Based on the four-component segmentation, histogram classification and standard hippocampus anatomy template, suspicious HS lesions were identified. The area of marked suspicious HS lesions was utilized for further quantitative analysis.

Detailed Definitions-based Clinical Information and Imaging Analysis

Patients were defined as unilateral MTLE if there was high concordance of epileptogenic lateralization and localization based on seizure semiology, unitemporal interictal spikes (defined as a ratio of > 80% of spikes occurring over the more affected temporal lobe), and ictal EEG pattern pointing to one temporal lobe. We defined the patients as bilateral MTLE if the recorded seizures arose from the bilateral temporal lobes independently based on semiology, ictal EEG pattern and bilateral temporal lobe spikes interictally.

The diagnosis using reconstructed data included the following steps: (i) T_1 and T_2 maps obtained by MRF were registered with corresponding acquired FLAIR, T_1-and T_2-weighted images with SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8) using 3D rigid body registration algorithm and the mutual information cost function. (ii) T_1 and T_2 values of normal hippocampal regions and suspicious regions marked by rTF-MRF of all patients were collected. (iii) The quantitative data of both patients and healthy controls were statistically analyzed for comparison. (iv) Two experienced epileptologists (WK and WDC, with experience in epileptology of 15 and 7 years, respectively) evaluated the statistical results of the hippocampi, registered MRF maps, tissue-fractional maps, FLAIR sequences, and T_1-and T_2-weighted images for detecting possible regions of HS. To validate the accuracy and sensitivity of MRF analysis, two coauthors WK and WDC who are senior epileptologists with experience in epileptology of 15 and 7 years, respectively, performed a double-blind test. All images were anonymized, and the two epileptologists did not know the final diagnosis based on extensive presurgical workup including scalp-video EEG monitoring and PET. They evaluated the anonymized images from the patients and the healthy controls within one day independently one month after the completion of recruitment. When there were disagreements on a given subject by visual inspection, they resorted to MRF-based quantification to reach a consensus.

Figure E1: Tissue fraction segmentations in transverse orientation of cerebrospinal fluid (CSF), gray matter, white matter and suspicious component with magnetic resonance fingerprinting (MRF) results in **(a)** a healthy control (37 years old, Male) and **(c)** a typical unilateral patient (S25, 44 years old, Male). White arrow in **(c)** is the segmented suspicious lesions. Histograms of T_1 and T_2 in the healthy control **(b)** and the typical unilateral patient **(d)** are presented.

Figure E2: (a) Transverse position of T1-weighted magnetization-prepared rapid gradient echo (MPRAGE), T2 weighted turbo spin-echo and T_1&T_2 maps obtained by magnetic resonance fingerprinting (MRF) in a typical unilateral patient (S18, 60 years old, Male). Black arrows indicate the possible hippocampal sclerosis (HS) lesions. **(b)** Boxplots of HS lesion and contralateral hippocampus.